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Novel predictors of infection-related rehospitalization in older patients with heart failure in Japan

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Aim: Rehospitalization of patients with heart failure (HF) incurs high health care costs and increased mortality. Infection-related rehospitalizations in patients with HF occur frequently, and the risk increases with age. This study aimed to identify the factors associated with infection-related rehospitalizations in older patients with HF.

Methods: Demographic, clinical, and pharmacological data from 1061 patients with acute HF who were enrolled in the Kochi Registry of Subjects With Acute Decompensated Heart Failure (Kochi YOSACOI study) were analyzed. Additionally, a machine learning approach was applied in addition to the traditional statistical analysis model. Of the patients hospitalized for HF, 729 were ultimately analyzed.

Results: During the 2-year postdischarge follow-up period, 121 (17%) patients were readmitted for infections. Logistic regression analysis identified a Japanese Cardiovascular Health Study (J-CHS) score of ≥3 (odds ratio, 1.83 [95% confidence interval, 1.18–2.83]; $P = 0.007$) at discharge as a key factor for infection-related rehospitalizations. Machine learning models confirmed that a higher J-CHS score and lower estimated glomerular filtration rate (eGFR) increased the risk of infection-related rehospitalizations. Decision tree analysis classified the risk into high (J-CHS score ≥3), medium (J-CHS score <3; eGFR ≤35.0) and low (J-CHS score <3; eGFR >35.0) groups.

Conclusions: Infection-related rehospitalizations occur in older patients with HF and are associated with frailty and eGFR. These findings provide valuable insights for health care providers to better manage the risk of infection-related rehospitalizations in older patients with HF, potentially improving patient outcomes. **Geriatr Gerontol Int 2025; 25: 543–552.**

Keywords: decision tree, frail, heart failure, infection-related rehospitalization, J-CHS score.

Introduction

Heart failure (HF) poses a substantial financial burden on health care systems worldwide due to its high incidence, fatality and frequent associated rehospitalizations.[1–5] Addressing readmissions is important because the high readmission rates in patients with HF increase health care costs and mortality.[6,7]

Infection-related rehospitalizations are common among patients with heart failure (HF),[8,9] with their incidence increasing with age.[10,11] In many developed countries, the number of older patients with HF[12–14] is rising due to aging populations. Consequently, infection-related rehospitalizations rates are expected to increase among older HF patients. Japan, home to one of the world's largest aging populations, has seen a significant increase in the number of older patients with HF. However, studies have specifically examined young patients with HF in their 60s and 70s[8,15] nor have they explored the factors associated with infection-related rehospitalizations in older patients aged >80 years HF, a group increasingly seen in real-world clinical practice. Identifying predictors of infection-related rehospitalizations in older patients with HF could be instrumental in reducing rehospitalization rates and improving clinical outcomes.[16]

Using data from the Kochi Prefecture Registry of Acute Heart Failure Patients (Kochi YOSACOI study) in Japan with a particularly aging population,[17,18] we applied new game theory–based methods in explainable machine learning, as well as the traditional statistical analysis models, to identify factors associated with readmission due to infection in older patients with HF.[19,20] In addition, using the identified risk factors, hierarchical shallow decision tree analysis was performed to determine the cutoff values for providing a risk indicator for readmission due to infection that would be useful in clinical practice.

Methods

Patient population

We drew upon data from the Kochi YOSACOI study, which enrolled 1061 patients with acute decompensated heart failure (ADHF) in Kochi, Japan, between May 2017 and December 2019. Furthermore, we included data on clinical outcomes for all-cause mortality, cardiac death and noncardiac death within 2 years, with follow-ups extending through December 2021. The Kochi YOSACOI study details have been previously described.[14] The Kochi YOSACOI study was a collaborative effort among six hospitals in Kochi Prefecture, Japan, all specializing in acute cardiovascular care. This prefecture has a notably high proportion of residents aged ≥65 years, accounting for 35% of the population. Additionally, all participating hospitals followed standardized guidelines for treating acute HF.[21] Individuals were eligible for enrollment if they were aged ≥20 years and receiving treatment for ADHF at one of the participating hospitals. The Framingham criteria were used to[22] diagnose ADHF, requiring the presence of at least two major criteria—such as findings from physical examinations, chest radiographs, or echocardiography—or one major criterion combined with two minor ones. The clinical characteristics of the patients have been extensively detailed in a previous study.[14] The investigators of the participating hospitals collected the data during the enrollment period. During the enrollment period, angiotensin receptor–neprilysin inhibitor and sodium–glucose cotransporter-2 inhibitors were not authorized for use in Japan.[23]

This study was authorized by the Medical Research Ethics Committee at the Kochi University of Medical Science (Approval No. 28-68) and Medical Research Ethics Committee at the Tokushima University Graduate School of Biomedical Sciences (Approval No. Z120). This study adhered to the principles of the Declaration of Helsinki, and informed consent was obtained from all the patients or their legal representatives.

Definition of infection-related readmission and patient selection

We defined infection-related readmission as hospital readmission due to pneumonia, urinary tract infection, or other infection-related events occurring after discharge following the completion of HF treatment.[8] Infection-related rehospitalizations were monitored for up to 2 years after discharge. In the initial patient cohort ($n = 1061$), we excluded 30 patients who died during hospitalization and 302 with missing data on left ventricular ejection fraction ($n = 108$), the Japanese Cardiovascular Health Study (J-CHS) score ($n = 107$), Geriatric Nutritional Risk Index (GNRI; $n = 4$) or other test findings ($n = 83$). The remaining 729 patients were categorized into two groups: those readmitted due to infection-related events during postdischarge follow-up ($n = 121$) and those not readmitted for such events ($n = 608$; Fig. S1).[15]

Measurements

Information concerning patient demographics, hospitalization symptoms, vital signs at discharge, laboratory and echocardiographic data, medical history, medication at discharge, lifestyle factors such as smoking and habitual drinking, socio-environmental factors such as living environment and place of residence and other relevant clinical parameters was collected. Echocardiographic data used in this study were obtained after the stabilization of patients' HF status during hospitalization. These data were collected through a study-specific questionnaire and hospital records.[14] Nutritional status was assessed using the GNRI, a simple measure for evaluating nutritional status of the elderly, calculated using this formula: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × body mass index/22.[24] Physical frailty was assessed using the J-CHS score, a straightforward method to assess frailty in older Japanese patients.[25] The J-CHS score was determined on the basis of the presence of any of the following five criteria[25]:

1. Slow walking speed: Defined as <1.0 m/s.
2. Muscle weakness: Assessed via maximum grip strength, with cutoff values of <26 kg for men and <18 kg for women.
3. Exhaustion: Identified if participants responded "yes" to the question, "Have you been feeling inexplicably tired for the past 2 weeks?"
4. Low activity: Determined if participants answered "no" to the question, "Do you do low-level exercise for health purposes?"
5. Weight loss: Evaluated if participants answered "yes" to the question, "Have you lost 2 kg or more in the past 6 months?"

Statistical analysis

All values are presented as medians with interquartile ranges for nonnormally distributed variables or as frequencies (percentages) for categorical variables. Student's *t*-test or the Mann–Whitney *U* test was performed to assess any differences in continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using logistic regression analysis. First, for the patients in both study groups, univariate analysis was performed on patient characteristics, HF symptoms at discharge, vital signs at discharge, laboratory and echocardiographic data, medical history, medications at discharge, lifestyle factors such as smoking and habitual alcohol consumption and other relevant clinical parameters. Next, logistic regression analysis was performed to examine patient characteristics (age and sex), factors having significant differences ($P < 0.05$) in univariate analysis and items that were associated as explanatory variables in previous studies, with the outcome being the presence of infection-related rehospitalizations. However, the factors that were suspected to have multicollinearity were excluded from the explanatory variables. A predictive model was constructed using items from the group comparisons. The interactions of each item were also examined. Finally, a decision tree with a shallow hierarchy was created to obtain a cutoff value to be used as a simple risk assessment index in clinical practice. Variables were selected on the basis of factors having a P-value of <0.1 in univariate analysis and factors that were associated with infection-related rehospitalizations in a previous study.[15] The presence of infection-related rehospitalizations was used as an indicator for decision tree analysis, and categorical and regression tree methods were used to stratify risk by combining multiple predictors. The variance inflation factor (VIF) was calculated to assess multicollinearity, and items with high values were excluded from the logistic regression analysis. A P-value of <0.05 was considered statistically significant in all tests. As part of sensitivity analysis, missing values were imputed using multiple imputation methods via multivariate imputation by chained equations.

To examine nonlinear relationships and interactions among the risk factors associated with infection-related rehospitalization in patients with HF via a machine learning model, we used the Light Gradient Boosting Machine, which is a type of Gradient Boosting Decision Tree (GBDT).[16] Machine learning techniques enable researchers to identify critical variables, including hidden interactions and patterns in the data that impact patient outcomes. These may not be readily discovered through conventional statistical methods.[26] We created an infection-related rehospitalization prediction model for patients with HF by employing previously mentioned variables as explanatory factors and defining infection-related rehospitalization as the target variable. Machine learning models are well known for their high predictive accuracy, although they can result in overfitting. Overfitting occurs when a model performs exceptionally well on the data used for its development but cannot easily predict novel data. To minimize this risk, it is crucial to evaluate the model performance on an independent dataset. Therefore, when constructing the mortality prediction model, we divided the dataset randomly into 80% for model development and reserved the remaining 20% for validation. We assessed the machine learning models using accuracy verification data and confirmed that the model developed in this study was unlikely to exhibit overfitting. Specifically, the evaluation was conducted using area under the curve, Youden index and sensitivity and specificity metrics when applied to the validation data set.

We utilized Shapley additive explanation (SHAP) values to quantify the effects of feature interactions.[27] SHAP interaction plots were used to clearly show how the probability of infection-related rehospitalization and target variable affect predictions. Our statistical analyses were performed using R version 4.2.0 (R Foundation for Statistical Computing; http://www.Rproject.org) and Python version 3.8.10 (Python Software Foundation; https://www.python.org).

Results

Patient characteristics

A complete analysis was conducted on 729 patients with HF. The median age of these patients was 81 years (interquartile range, 72.0–86.0; Table 1). During the 2-year follow-up period after discharge, 121 patients (17%) experienced infection-related readmissions, among whom 63 (52.1%) had pneumonia, 27 (22.3%) had urinary tract infection and 31 (25.6%) had other infections (Table S1). The patients were categorized into two groups: those readmitted due to infection-related events during the postdischarge follow-up ($n = 121$) and those without infection-related rehospitalizations ($n = 608$). Patients with HF who experienced infection-related rehospitalizations were older; had lower GNRI, albumin and hemoglobin levels at discharge; had higher J-CHS scores; had a higher prevalence of cerebrovascular disease history and were less frequently prescribed beta-blockers at discharge.

Predictors of infection-related rehospitalization

Factors associated with infection-related rehospitalizations in patients with HF were examined (Table 2). Multivariate analysis identified a J-CHS score of ≥3 (OR, 1.83 [95% CI, 1.18–2.83]; $P = 0.007$) as an independent predictor of infection-related rehospitalizations. However, GNRI and albumin levels showed potential multicollinearity (VIF, 2.7 and 2.6, respectively), leading to the exclusion of albumin level, which had a higher VIF value, from the explanatory variables. Additionally, a logistic regression model using the multiple imputation method for missing values revealed significant ORs for a J-CHS score of ≥3 (OR, 1.76 [95% CI, 1.18–2.64]; $P = 0.007$; Table S2).

Analysis of the machine learning model

To predict the probability of infection-related readmission, a GBDT model was constructed for each patient. SHAP values were calculated for each patient-derived model to quantify feature importance and interaction effects. Calculation and ranking of SHAP values for each variable in the patient data revealed that the J-CHS score and low estimated glomerular filtration rate (eGFR) were the most important features in predicting increased infection-related readmission rates (Fig. 1). By calculating the probability of infection-related rehospitalization by J-CHS score and eGFR, an increased risk was observed with J-CHS scores of >3 and SHAP values of <35 for eGFR (Figure 2a,b). The area under the curve of the constructed GBDT model applied to the verification data was 0.686. The Youden index was 0.320, with a sensitivity of 0.489 and specificity of 0.831.

Interactions between age and J-CHS score

We examined whether the interaction effect of the J-CHS score affects the predicted probability of infection-related rehospitalization based on age; the SHAP interaction value (y axis) as a function of patient age (x axis) was plotted with the interaction variable value indicated by the dot color (red, for a J-CHS score of ≥3 and blue for a J-CHS score of <2). The results revealed an interaction between age and the J-CHS score (Fig. 2c). Patients aged ≥80 years had a different risk of rehospitalization due to infection according to a J-CHS score of ≥3. In particular, a J-CHS score of ≥3 increased the risk of readmission due to infection in patients aged ≥80 years.

Decision tree analysis

A shallow hierarchical decision tree was created, and cutoff values were obtained to provide a simple risk assessment index for clinical practice. As shown in Figure 3, the decision tree analysis stratified the probability of infection-related rehospitalization into three groups based on the J-CHS score and eGFR: high risk (J-CHS

Table 1 Baseline characteristics of the study patients

	All patients (n = 729)	Patients with infection-related rehospitalization (n = 121)	Patients without infection-related rehospitalization (n = 608)	P-value
Age (years)	81.0 [72.0–86.0]	83.0 [76.0–88.0]	81.0 [71.0–86.0]	0.007*
Female	356 (48.8)	53 (43.8)	303 (49.8)	0.266
BMI (kg/m^2)	21.0 [18.8–23.3]	20.6 [18.3–22.7]	21.1 [18.9–23.6]	0.124
GNRI	91.4 [84.6–98.7]	89.9 [81.6–97.1]	91.6 [85.4–99.1]	0.017*
NYHA class III/IV at discharge	6 (0.8)	1 (0.8)	5 (0.8)	0.999
Laboratory data at discharge				
Albumin (g/dL)	3.5 [3.1–3.7]	3.3 [3.1–3.6]	3.5 [3.1–3.8]	0.014*
BNP (pg/mL)	276.7 [142.0–500.1]	356.0 [150.0–567.0]	262.0 [141.5–477.5]	0.051
eGFR (mL/min/1.73 m^2)	44.6 [32.1–60.0]	44.4 [27.7–57.5]	44.7 [33.2–60.6]	0.055
Hemoglobin (g/dL)	11.6 [10.1–13.2]	11.1 [9.6–12.2]	11.6 [10.1–13.2]	0.003*
Sodium (mEq/L)	139.0 [137.0–141.0]	139.0 [137.0–141.0]	139.0 [137.0–141.0]	0.972
SBP at discharge	112.0 [100.0–125.0]	116.0 [101.0–126.3]	112.0 [100.0–125.0]	0.164
Echocardiographic parameters at discharge				
LVEF (%)	48.0 [34.0–62.0]	50.0 [35.5–65.0]	48.0 [34.0–61.4]	0.196
Frailty assessment				
J-CHS score	3 [2–3]	3 [2–4]	3 [2–3]	<0.001*
1	101 (13.8)	10 (8.3)	90 (14.8)	0.113
2	203 (27.8)	25 (20.7)	178 (29.3)	0.059
≥3	395 (54.0)	83 (68.6)	311 (51.2)	<0.001*
Components of J-CHF score				
Slow walking speed	0.74 [0.52–0.98]	0.77 [0.52–1.00]	0.66 [0.50–0.82]	0.001*
Weakness	18.6 [13.3–26.0]	17.9 [13.0–23.3]	18.7 [13.3–26.7]	0.254
Low activity	305 (41.8)	52 (43.3)	253 (41.6)	0.762
Fatigue	192 (26.3)	26 (21.5)	166 (27.4)	0.214
Weight loss	140 (19.2)	28 (23.1)	112 (18.5)	0.256
Underlying disease				
Hypertension	544 (74.6)	92 (76.0)	452 (74.3)	0.783
Atrial fibrillation	343 (47.1)	57 (47.1)	286 (47.0)	0.999
Dyslipidemia	323 (44.3)	60 (49.6)	263 (43.3)	0.238
Diabetes mellitus	221 (30.3)	40 (33.1)	181 (29.8)	0.542
Cerebrovascular accident	125 (17.1)	30 (24.8)	95 (15.6)	0.021*
Old myocardial infarction	124 (17.0)	19 (15.7)	105 (17.3)	0.774
Dementia	118 (16.2)	14 (11.6)	104 (17.1)	0.169
COPD	68 (9.3)	15 (12.4)	53 (8.7)	0.271
Bronchial asthma	39 (5.3)	8 (6.6)	31 (5.1)	0.650
Medication at discharge				
Beta-blockers	455 (62.4)	63 (52.1)	392 (64.5)	0.013*
RAS inhibitors	356 (48.8)	54 (44.6)	302 (49.7)	0.361
MRAs	276 (37.9)	36 (29.8)	240 (39.5)	0.056
Loop diuretics	650 (89.2)	105 (86.8)	545 (89.6)	0.445
Thiazide diuretics	36 (4.9)	8 (6.6)	28 (4.6)	0.36
Calcium channel blockers	251 (34.3)	46 (38.0)	205 (33.7)	0.421
Digitalis	2 (0.3)	1 (0.8)	1 (0.2)	0.749
Anticoagulants	275 (37.7)	51 (42.1)	224 (36.8)	0.319
Habits				
Habitual drinking	140 (19.2)	18 (14.9)	122 (20.1)	0.416
Current smoking	92 (12.6)	10 (8.3)	82 (13.5)	0.416
Living environment				
With family	284 (39.0)	53 (43.8)	231 (38.0)	0.405
Partner only	203 (27.8)	28 (23.1)	175 (28.8)	0.114
Living alone	180 (24.7)	34 (28.1)	146 (24.0)	0.487

(*Continues*)

Table 1 Continued

	All patients ($n = 729$)	Patients with infection-related rehospitalization ($n = 121$)	Patients without infection-related rehospitalization ($n = 608$)	P-value
Place of residence				
Home	666 (91.4)	112 (93.3)	554 (91.3)	0.589
Nursing home	44 (6.0)	7 (5.8)	37 (6.1)	0.999
Other hospitals	17 (2.3)	1 (0.8)	16 (2.6)	0.333

Data are shown as median [interquartile range] or n (%).

ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; J-CHS, Japanese Cardiovascular Health Study; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAS, renin–angiotensin system; SBP, systolic blood pressure.

*Denotes a significant difference.

Table 2 Predictors of infection-related hospitalization in patients with heart failure

Category	Crude OR (95% CI)	Adjusted OR (95% CI)	P-value
J-CHS score ≥3	2.03 (1.35–3.07)	1.83 (1.18–2.83)	0.007*
Cerebrovascular accident	1.83 (1.15–2.91)	1.49 (0.92–2.42)	0.108
Diabetes mellitus	1.15 (0.76–1.75)	1.18 (0.76–1.83)	0.462
RAS inhibitors	0.83 (0.56–1.23)	1.07 (0.70–1.63)	0.766
Age (years)	1.02 (1.00–1.04)	1.01 (0.99–1.03)	0.394
Hemoglobin (g/dL)	1.00 (1.00–1.01)	1.00 (0.99–1.02)	0.382
eGFR (mL/min/1.73 m^2)	0.98 (0.98–1.01)	0.99 (0.98–1.01)	0.201
GNRI	0.98 (0.97–1.00)	0.99 (0.97–1.01)	0.289
Loop diuretics	0.77 (0.43–1.38)	0.86 (0.46–1.59)	0.631
Female	0.77 (0.52–1.14)	0.73 (0.48–1.10)	0.134
Beta-blockers	0.61 (0.41–0.90)	0.67 (0.44–1.02)	0.064

Data are shown as median [interquartile range] or n (%).

CI, confidence interval; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; J-CHS, Japanese Cardiovascular Health Study; OR, odds ratio; RAS, renin–angiotensin system.

*Denotes a significant difference.

score ≥3, $n = 394$), medium risk (J-CHS score <3; eGFR ≤35.0; $n = 83$) and low risk (J-CHS score <3; eGFR >35.0; $n = 252$).

Discussion

This multicenter prospective cohort study revealed that in older patients with HF, the J-CHS score and eGFR at discharge were associated with infection-related rehospitalizations. Moreover, the machine learning models revealed that a higher J-CHS score and lower eGFR were associated with an increased risk of infection-related rehospitalizations; an interaction was observed between the J-CHS score and age. Finally, decision tree analysis categorized the risk of infection-related rehospitalizations into three groups based on the J-CHS score and eGFR, with thresholds of ≥3 and <35, respectively.

Patients with HF are more susceptible to infections, which are major causes of rehospitalization in patients with HF.[8,15,28] Rehospitalizations due to infections are associated with high mortality rates and poor long-term outcomes.[8,29] Given the significant impact on patient prognosis, management of infections in patients with HF to improve overall outcomes is critical. Predictors of infection-related rehospitalizations in patients with HF include older age, female sex, chronic obstructive pulmonary disease, previous myocardial infarction, diabetes, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker administration and low hemoglobin levels.[8,15] However, these reported predictors are suitable for relatively young patients with HF in their 50s to 70s. They may differ from the predictors of infection-related rehospitalizations in older patients with HF, and its incidence has recently been increasing worldwide.[12–14] In this study, we examined the factors associated with infection-related rehospitalization in older patients with HF using data from the Kochi YOSACOI study, which was conducted in an area of Japan with a particularly aging population. Compared with the factors associated with infection-related rehospitalizations in younger patients with HF, those in older patients with HF were related to a higher extent to physical features such as frailty and impaired renal function. Studies have only identified individual risk factors such as age, sex or comorbidities associated with infection-related readmissions.[8,15] In contrast, this study was able to stratify risk by integrating multiple factors, representing a novel finding. This stratification enables the development of tailored interventions for each risk stratum. Furthermore, the combination of traditional statistical analysis with machine learning modeling has enhanced the study's reliability and applicability, yielding valuable insights that may contribute to improved outcomes for older patients with HF.

Frailty is a common symptom in older patients with HF,[30,31] although patients with frailty symptoms have compromised immune systems and are at higher risk of infections.[32] In this

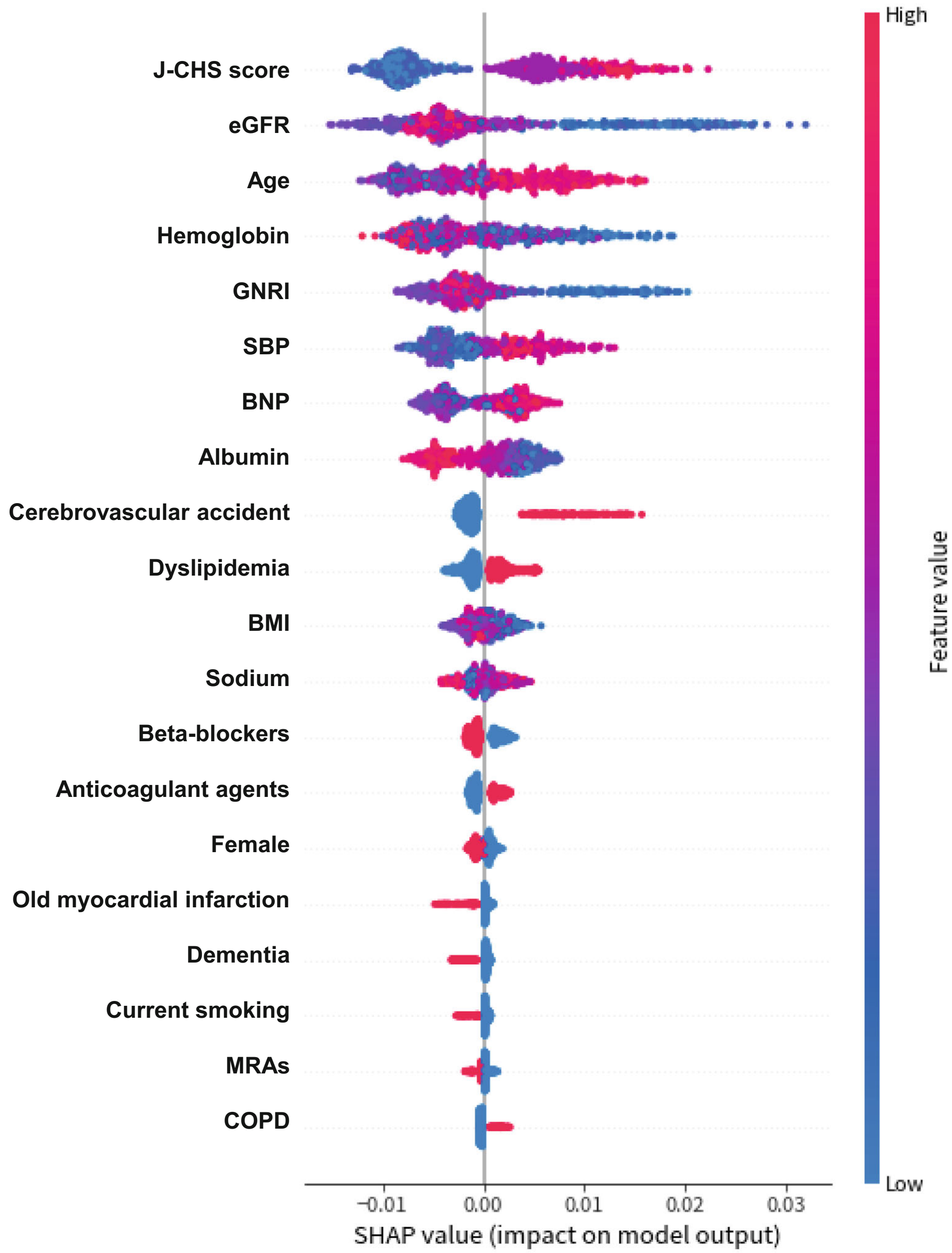

Figure 1 Shapley additive explanation (SHAP) values for each variable were calculated from the individual values of each patient within the prediction model. Each data point is represented by a dot with a color based on the variable value. The red dots indicate high values for a particular patient's variable, whereas the blue dots indicate low values. For binary categorical variables, a blue dot indicates the absence of the category, and a red dot indicates its presence. By visualizing these patient-specific SHAP values, the relationship between the value of each variable (indicated by the dot color) and its impact on the model output becomes clear. BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; J-CHS, Japanese Cardiovascular Health Study; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

study, pneumonia (52.1%) and urinary tract infection (22.3%) were the most common infectious diseases among patients hospitalized for infection-related diseases (Table S1). Frailty in older individuals is significantly associated with an increased incidence of pneumonia,[33] especially in patients with HF, as alveolar flooding and reduced microbial clearance may increase the risk of pneumonia.[34] Patients with frailty are also at a significantly higher risk of developing urinary tract infections.[35] Decreased renal function increases the risk of urinary tract infections,[36] especially in older patients with HF who often have decreased renal function, which may have further increased the risk of urinary tract infections.

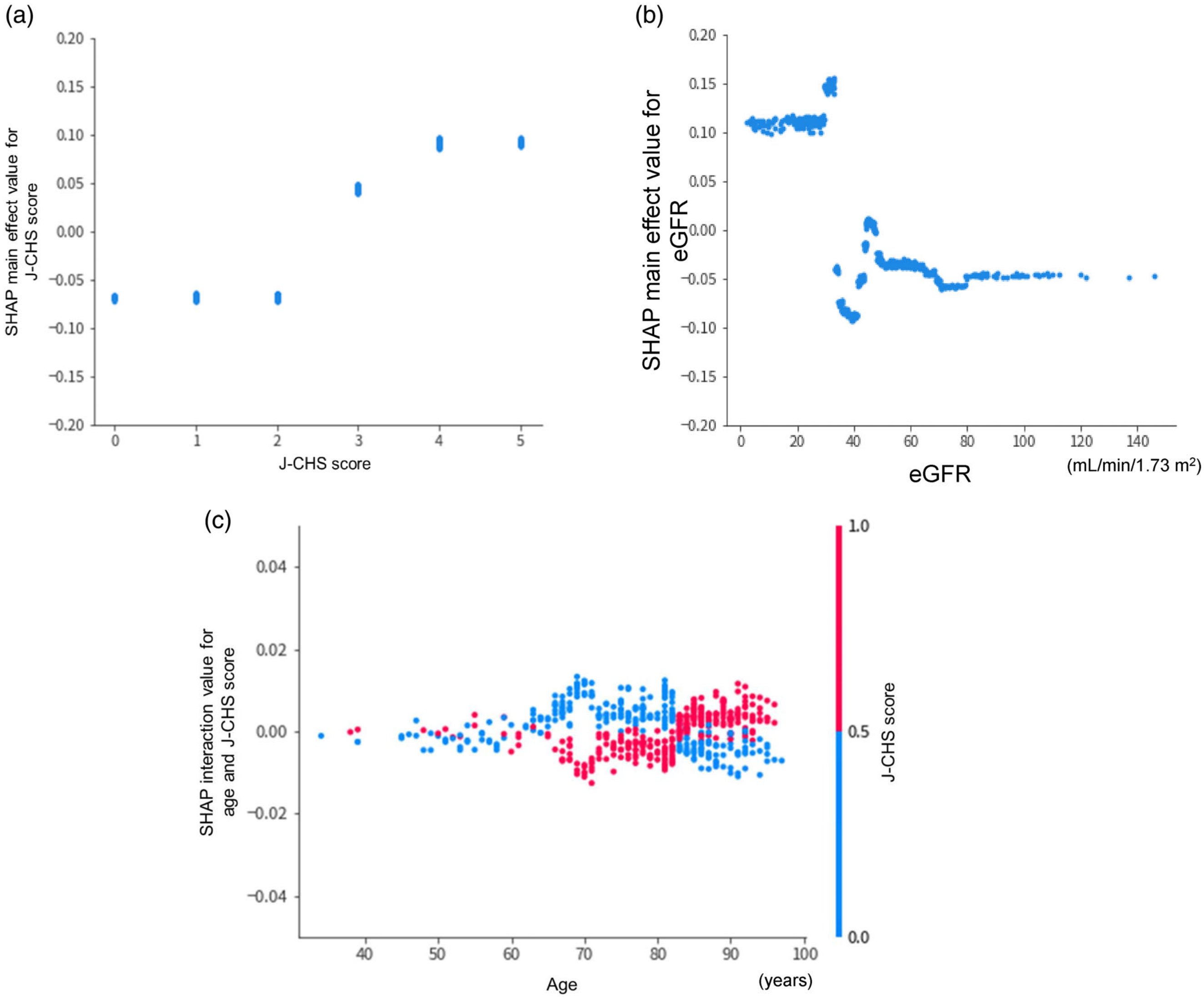

Figure 2 Shapley additive explanation (SHAP) main effect value for the (a) Japanese Cardiovascular Health Study (J-CHS) score and (b) estimated glomerular filtration rate (eGFR). SHAP values for each variable were calculated from the individual values of each patient within the prediction model. Each data point is represented by a dot with a color based on the variable value. By visualizing these patient-specific SHAP values, the relationship between each variable value (indicated by the dot color) and its impact on the model output becomes clear. (c) The interaction effects of J-CHS score influence the predicted probability of infection-related hospitalization based on age. The SHAP interaction values quantify these effects and show the interaction between age and the J-CHS score. When the SHAP interaction values (*y* axis) are plotted as a function of patient age (*x* axis) and the value of the interacting variable (indicated by the color of the dot—red for a J-CHS score of ≥3 and blue for a J-CHS score of <2), trends in variables and their values that have a greater interaction effect emerge. In the case of age, an interaction effect with a J-CHS score of ≥3 becomes apparent at approximately 80 years of age.

In our study, an interaction between frailty and age was observed. Older age has a strong influence on frailty and subsequent infections. This result is consistent with the fact that frailty is a strong risk factor in our predominantly older study population; in contrast, it was not identified as a strong risk factor in a study with younger patients.[14] Another study did not include frailty as a potential risk factor.[15] This may be attributed to the fact that frailty is less common in young adults. As people age, their health status depends more on their physical condition than on their actual age. Compared with chronological age, frailty may better indicate infection risk, as it may indicate physical decline. While past literature has focused on individual health elements, such as a low hemoglobin level, diabetes mellitus and obstructive lung disease,[15] frailty is associated with many of these elements and may truly indicate "unhealthiness" that encompasses these factors. Therefore, frailty may be more strongly associated with the risk of infection than these individual factors. Among the components of the J-CHF score in this study, walking speed was associated with infection-related rehospitalizations. Walking speed is widely recognized as an indicator of frailty in older adults.[37] Therefore, measuring gait speed may serve as a useful tool for predicting infection-related rehospitalizations in older patients with HF. The interaction between age and J-CHS score observed in this study highlights that the risk of infection-related

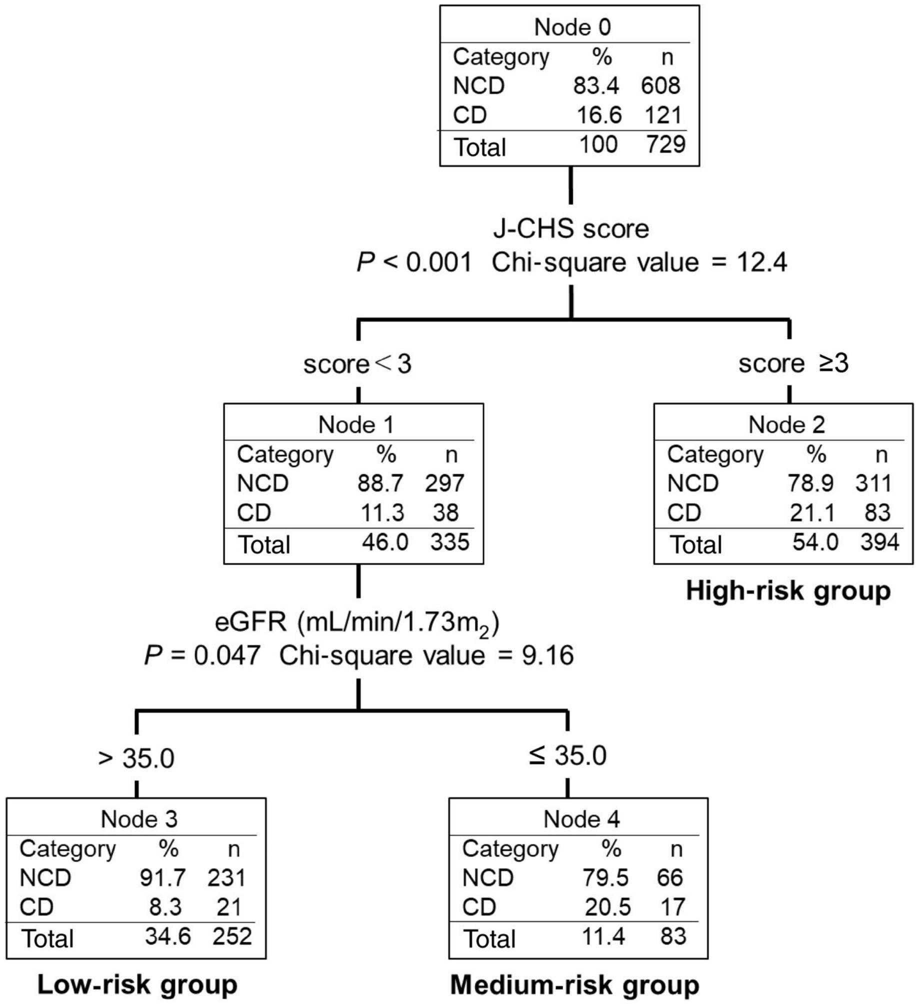

Figure 3 Decision tree analysis used to stratify the probability of infection-related hospitalization. Patients were classified into the high-risk (Japanese Cardiovascular Health Study [J-CHS] score ≥3; $n = 394$), medium-risk (J-CHS score <3; eGFR ≤35.0; $n = 83$) and low-risk groups (J-CHS score <3; eGFR >35.0; $n = 252$). CDs, cardiovascular deaths; eGFR, estimated glomerular filtration rate; NCDs, non-cardiovascular deaths.

hospitalization increases substantially when frailty is present in individuals aged ≥80 years, underscoring the importance of targeted interventions for this group. While age is a nonmodifiable factor, frailty can be improved or prevented through proactive measures. Rehabilitation, exercise programs and nutritional management are critical strategies to address frailty in this population.[38–40] Additionally, enhancing social support is vital to ensure access to these interventions as older adults are often socially isolated, living alone or experiencing cognitive impairments; this can hinder the delivery of effective care. For patients at high risk of infection, such as older individuals with HF and existing frailty, management strategies should include preventative measures including vaccination against pneumococcus, influenza and COVID-19, as well as implementing and reinforcing oral care.[41–43] These approaches may contribute to reducing infection-related readmissions.

Decision tree analysis revealed that a high J-CHS score (≥3) indicates a high risk of rehospitalization due to infection, irrespective of eGFR, whereas a J-CHS score of <2 is associated with medium or low risk depending on eGFR. These findings suggest that frailty is a significant factor linked to infection-related rehospitalizations in patients with HF, potentially encompassing the condition of impaired renal function.[14] Frailty results from immune aging, which diminishes both acquired and innate immunity, thereby increasing susceptibility to infections, even from pathogens that would not normally cause illness.[32,44] Consequently, frailty itself is as an absolute risk factor that places individuals at a consistently high risk of infection. Conversely, those without frailty typically have normal immune function and are at a lower risk of infection during normal pathogen exposure. However, when renal dysfunction is present, the local clearance of pathogens, such as in the lungs or urinary tract, becomes impaired, increasing the likelihood of infection. Poor renal function exacerbates the risk of infection and infection-related rehospitalizations.[45] In patients with HF, reduced renal function increases the risk of pulmonary congestion, which can impair sputum clearance and predispose to pneumonia.[46] This creates a vicious cycle wherein infections including pneumonia further deteriorate renal function through immune-mediated mechanisms.[47] As renal function declines, diuretics become less effective,[48] leading to worsened HF. This progression further impairs sputum clearance, increasing the risk of pneumonia. For HF patients without frailty, impaired renal function may predict infection-related rehospitalizations. Conversely, the risk of such rehospitalizations is relatively low in older patients with HF without frailty and with preserved renal function. These findings underscore the importance of preventing frailty and preserving renal function in older patients with HF, whose population is expected to increase in the future.

This study has several limitations. First, while significant covariates were accounted for, this was an observational study; thus, unmeasured confounding variables may have influenced the results. For example, vaccination, an important factor in infection prevention, was not assessed, and vaccination effects were beyond the study's scope. Additionally, socioeconomic factors that could impact infection-related rehospitalizations were not assessed. Second, the mechanisms by which frailty and impaired renal function increase infection-related rehospitalizations could not be determined due to the observational nature of the study. Third, compared to previous research, the Kochi YOSACOI study included an older population with a median age of 81 years, limiting the generalizability of these findings to all patients with HF. However, the Kochi YOSACOI study was well suited to investigate age-related symptoms, given its sample size and demographic composition. Fourth, while the Kochi YOSACOI study attempted to distinguish between readmissions caused by infections and other causes, it might have missed patients who developed infections during hospitalization for worsening HF or those who died at home from infections. Finally, the risk classification model for infection-related rehospitalizations proposed in this study has not been externally validated. Therefore, its applicability to predict rehospitalizations in other patient populations remains uncertain. Future prospective studies are required to validate this model and its applicability to broader patient groups.

Conclusions

This study revealed that a reasonable number of patients with HF were rehospitalized due to infection and suggested that comorbid frailty and impaired renal function increase the risk of infection-related rehospitalizations in older patients with HF. The number of older patients with HF is expected to increase in the future; thus, these findings may provide useful insights into the management of older patients with HF.

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Disclosure statement

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Author contributions

K.K.: Conceptualization, Methodology, Investigation, Writing—Original Draft. T.I.: Methodology, Validation, Formal Analysis, Writing—Review and Editing. H.F.: Conceptualization, Writing—Review and Editing. Y.H.: Methodology, Writing—Review and Editing, Statistical Analysis. T.K.: Investigation, Writing—Review and Editing. T.H.: Investigation, Writing—Review and Editing. Y.B.: Writing—Review and Editing. F.A.: Writing—Review and Editing. K.Y.: Writing—Review and Editing. Y.I.: Writing—Review & Editing. T.N.: Writing—Review and Editing. S.A.: Writing—Review and Editing. M.G.: Conceptualization, Writing—Review and Editing. H.K.: Supervision, Funding Acquisition, Writing—Review and Editing. K.I.: Project Administration, Writing—Review and Editing.

Data availability statement

The deidentified participant data associated with this study will not be shared.

Ethics statement

This study was authorized by the Medical Research Ethics Committee at Kochi University of Medical Science (Approval No. 28-68) and the Medical Research Ethics Committee at Tokushima University Graduate School of Biomedical Sciences (Approval No. Z120). This study adhered to the principles of the Declaration of Helsinki.

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Patient consent statement

Informed consent was obtained from all patients or their legal representatives.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Study flow chart: Patient selection and analysis process.

Table S1. Type of infection.

Table S2. Sensitivity analysis using the multiple assignment method.

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